REMARKS

This is a full and timely response to the Office Action mailed October 5, 2005, submitted concurrently with a two month extension of time to extend the due date for response to March 6, 2006.

The specification has been amended to clarify the Examiner's understanding. No claims have been amended in this response. Thus, claims 20-32 are currently pending in this application.

In view of this response, Applicants believe that all pending claims are in condition for allowance. Reexamination and reconsideration in light of the above amendments and the following remarks is respectfully requested.

Rejections under 35 U.S.C. §112

Claims 26 and 28 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicant respectfully traverses this rejection. However, in the interest of expediting the prosecution of the present application. Applicant has amended the specification to specify that *"[T]he amount of plasmid DNA added to the lipid film was 400 μg total DNA, and the total volume of plasmid DNA added to the lipid film was 1 ml."* Thus, withdrawal of this rejection is respectfully requested.

Claims 29-32 (not claim 1 since it has been canceled) are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicant respectfully traverses this rejection.

The Examiner has argued in the Office Action that the specification fails to provide adequate guidance on the prevention or treatment of influenza in humans. The Examiner has also stated that the vaccine has not been shown to be effective or safe in humans. Applicants respectfully disagree with the Examiner's conclusions in this regard.

Applicants believe that the specification clearly describes the manner and process of practicing the claimed invention in full, clear, concise and exact terms so as to enable one skilled in the art to make and use the present invention. In other words, one skilled in the art, based on the teachings of the specification and the knowledge in the art, can practice the method of the present invention without undue experimentation. As stated in § 2164.01(a) of the Manual of Patent Examining Procedure (MPEP), there are many factors to consider when determining

whether there is sufficient evidence to support a conclusion that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill,
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure

With regard to the breadth of the claims, claims 29-32 are directed to a method for preventing and/or treating influenza virus infection or for eliciting long-lasting protective antiviral immune responses against influenza viruses, comprising administering to a patient in need thereof a pharmaceutically effective amount of the composition of claim 20. Based on these claim limitations, the specification only needs to demonstrate that the claimed method would be sufficient to prevent or treat influenza virus infection. As shown in the Examples of the specification, upon administration of the composition of claimed invention, the effects of influenza virus infection was completely prevented.

As shown in the experimental results and discussed on page 10, lines 5-16, of the specification, the efficacy of the naked and liposome-encapsulated pCI-HA10 plasmids to protect animals against lethal challenge of influenza virus by intranasal and intramuscular administrations is shown in FIGS. 3 and 4. Non-immunized mice succumbed to the influenza infection at as early as 7 days post infection, and all animals were dead by day 9. All mice which received intranasal immunization with naked unencapsulated pCI-HA10 also succumbed to the infection, with no increase in survival rate nor survival time (FIG. 3). In contrast, mice immunized intranasally with liposome-encapsulated pCI-HA10 ***were found to be completely***

protected with 100% survival rate (p<0.01 vs. control or naked pCI-HA10 group). Further, when the pCI-HA10 DNA was administered by intramuscular injection, both liposome-encapsulated and naked pCI-HA10 plasmid were shown to provide complete protection against the virus challenge (FIG. 4). In contrast, liposome-encapsulated pCI without the HA insert provided little or no protection.

The Examiner has noted in the Office Action that the enabling disclosure is clearly not commensurate in scope with these claims. However, such a position is unduly restrictive and contrary to that expressed in the Manual of Patent Examining Procedure.

Under § 2164.01(c) of the MPEP, if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC § 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960). It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information can be obtained without undue experimentation.When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re* Vaeck, 947 F.2d 488, 495, 20 USPQ 2d 1438, 1444 (Fed. Cir. 1991).

Here, in this case, the animal models used in the Examples of the specification clearly support the limitations of the claims. It is well recognized in the art that the particular animal model of the specification correlates with the influenza virus infection in humans. In other words, Applicants submit that the animal model studies of the specification would be viewed by one skilled in the art as being reasonably predictive of the effectiveness of the present invention in treating or preventing influenza virus infection.

It is important to emphasize that the Federal Courts have consistently reversed rejections by the Patent Office asserting a lack of enablement for inventions claiming a pharmacological or

therapeutic use where Applicants have provided evidence that reasonably support such a use. As a general rule, evidence of pharmacological or other biological activity of a composition will be relevant to an asserted therapeutic use if there is a ***reasonable correlation*** between the activity of the composition and its asserted method of use. Applicants do not have to prove with statistical certainty that a correlation exist between a particular activity of a compound or composition and its therapeutic use. Further, Applicants also are not required to provide actual evidence of success in **treating humans** where such utility is asserted. Instead, as the Courts have repeatedly held, all that is required is a reasonable correlation between the activity of the compound or composition, and its asserted use.

Thus, if reasonably correlated to the particular therapeutic or pharmacological activity, data generated using *in vitro* assays or tests in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological use for the compound, composition or process. In other words, while an Applicant may need to provide evidence to show that the invention will work as claimed, it is improper for the Patent Office to question the ***"degree of effectiveness"*** of a claimed method and/or pharmaceutical composition. See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex Parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

As stated above, the disclosure and Examples of the specification clearly demonstrate the effectiveness of the claimed method in preventing and/or treating influenza virus infection in humans. Thus, for these reasons, Applicants believe that this rejection of claims 29-32 under 35 USC § 112, first paragraph, cannot be sustained and should be withdrawn.

Rejection under 35 U.S.C. §103

Claims 20-28 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Wheeler et al. and Webb et al. in view of Sha et al. and Promega Catalog. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the cited references, in combination, must teach or suggest the invention as a whole, including all the limitations of the claims. Here, in this case, the combination of Wheeler et al., Webb et al. in view of Sha et al. and Promega Catalog fails to teach the claimed liposomal vaccine composition (i.e. a plasmid **encapsulated within a liposome**) and the method of making thereof.

The Examiner argues that the present invention relating to the encapsulation of plasmid DNA follows essentially the method used by Wheeler et al. However, based on Applicant's thorough review of the cited references, Applicant believe that the method of encapsulation of the DNA vaccine of the present invention is clearly very different from the method used by Wheeler et al.

The method of encapsulation used in the present invention is known in the art as reverse phase rotary evaporation (RPRE) followed by detergent dialysis. The method employed by Wheeler et al. is detergent dialysis, not reverse phase rotary evaporation. In this RPRE method of the present application, the inventors generated a thin lipid film prior to the addition of the DNA vaccine. In contrast, in Wheeler et al., no lipid film was formed (see page 279, last paragraph, of Wheeler et al.).

More specifically, in Wheeler et al, the plasmid DNA was first mixed and incubated with the DODAC and detergent, prior to detergent dialysis (see page 279, line 1-6, last paragraph, of Wheeler et al.). In contrast, the methods used in this invention do not follow this procedure. Instead, the lipids were mixed and rotary evaporated to form a thin lipid film. Once the lipid film is formed, the detergent and the DNA vaccine were then added to the film for the reconstitution of the liposomes, followed by dialysis.

Further, the final preparation step taught by Wheeler et al. used a density gradient ultracentrifugation step for concentration of the liposomes, whereas in the present invention, the inventors used an Aquacide II resin followed by a polyethylene glycol concentration step.

With regard to the Webb et al. reference, the Examiner cites Webb et al. as a basis of rejection since the reference teaches the use of C8 ceramide. However, Applicants would like to point out that the PEG-ceramide is one of the unusual lipids used for the preparation of

liposomes. In Webb et al., it was used as one of the lipids for the encapsulation of an anti-cancer drug, vincristine. The method used in Webb et al. to entrap the anticancer drug is known as remote drug loading using a transmembrane pH gradient (see page 274, section 2.6, line 15-25, of Webb et al.). Hence, Webb et al. does not teach the use of the method of DNA encapsulation of the present invention, nor does it suggest that the entire plasmid DNA could be encapsulated within the liposomes using ceramide C8.

Further, Applicants also submit that there is no motivation in any of the cited references to modify or combine reference teachings. Under U.S. practice, to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. As noted in Applicant's earlier responses and arguments which the Examiner had found persuasive, a novel and unobvious aspect of the patent invention is that the DNA vaccine is encapsulated within the liposomes, and not complexed with the lipids. Since the application of the Webb et al. reference is for increasing the circulation time and the pharmacokinetics of the anticancer drug, vinersitine (see abstract, page 272, line 6-9, of Webb et al.) in the body and not about encapsulating plasmid DNA vaccine within liposomes, and avoiding DNA-lipocomplex formation, Applicant submits that there is insufficient motivation in the cited references to modify or combine reference teachings.

Thus, for these reasons, withdrawal of this rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, all the claims now pending in the present application are believed to be clearly patentable over the outstanding rejections. Accordingly, favorable reconsideration of the claims in light of the above remarks is courteously solicited. If the Examiner has any comments or suggestions that could place this application in even better form, the Examiner is requested to telephone the undersigned attorney at the below-listed number.

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Respectfully submitted,

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